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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,428	PETERS, LARS-ERIK	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-35 and 43-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-35 and 43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/19/2008 has been entered.

Status

Claims 15-35 and 43-47 are pending in the application.

The rejection under 35 U.S.C. 102(b) over Asada et al (WO 00/14218) is maintained against claims 15-19 for the reasons of record and set forth below.

The rejections under 35 U.S.C. 102(b) over Schinazi et al (Antimicrobial Agents and Chemotherapy 33(1):115-117 (1989)) and the rejections under 35 U.S.C. 103(a) based thereon are withdrawn in view of Applicant's amendment to claim 22 reciting that the solution lacks one of a template and a primer. Schinazi only taught the composition of the reverse transcriptase reaction, and so it cannot be said that the polymerase and the dextran sulfate were ever present in solution in the absence of either a template or a primer. For the same reasons, rejections under 35 U.S.C. 102(b) over Diringer (US 5,153,181) and the rejections under 35 U.S.C. 103(a) based thereon are likewise withdrawn.

The rejection of claims 22, 32-34 and 43-47 under 35 U.S.C. 103(a) over Asada (WO 00/14218) in view of Qiagen News (Issue No. 1, 1999) is maintained for the

reasons of record and as further explained below. In addition, this rejection has been applied to additional claims.

Any rejection not appearing below may be considered withdrawn as no longer applicable.

Applicant's arguments will be addressed following the rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Asada et al (WO 00/14218, the March 16, 2000 publication of international application PCT/JP99/04815) as evidenced by Uemori et al (USPN 6,673,578). As the Asada reference was published in Japanese, US Pat. 6,673,578 (which resulted from the national phase entry of PCT/JP99/04815 under 35 U.S.C. 371) will be used as an English translation, and all teachings will be pointed out with reference to the '578 patent.

Asada teaches both a composition for polynucleotide (i.e. DNA) synthesis (beginning at column 3, line 20) and a kit for use in practicing the method (beginning at column 12, line 33).

With regard to claim 15, Asada teaches a kit (column 12, line 33) comprising a thermostable polymerase (column 12, lines 40-45 and line 58; "Taq" is Thermus

aquaticus DNA polymerase, which is thermostable), a non-nucleic acid polyanion ("acidic substance"; column 13, lines 10-19 and column 9, lines 34-63; for example polyvinyl sulfates, polystyrene sulfates (column 9, line 38), sulfated-fucose-containing polysaccharides, dextran sulfate (column 9, lines 46-47)), and an appropriate polymerase reaction buffer (column 13, lines 31-34).

Asada also teaches:

> "Incidentally, as a composition of a reaction mixture, there may be used a reaction mixture having a composition suitable for DNA polymerase used. Here, the term "composition suitable for DNA polymerase" means a composition capable of providing optimum conditions such as optimum kinds of buffers, optimum pH, optimum salt concentration (magnesium salt, and the like), optimum dNTPs concentration, optimum amount of primers and other additives." (column 4, lines 10-20, emphasis provided)

Asada gives exemplary optimal concentrations of magnesium (2 mM, which is at least 1.5 mM) and potassium (50 mM, which is between about 35-100 mM; potassium is a monovalent cation). See column 4, lines 32-35.

Finally, Asada clearly states:

> "The above DNA polymerase, the acidic substance and other reagents may be contained in the kit in a state where each is present as an independent component, or a state in which some of the components are combined, including, for instance, a state in which the components are added to the reaction buffer and the like." (column 13, lines 34-39)

With regard to claim 16, Asada teaches Thermus aquaticus (i.e. Taq; column 12, lines 40-45 and line 58).

With regard to claim 17, Asada teaches dextran sulfate (column 9, lines 43-47).

With regard to claim 18, Asada teaches nucleotide 5'-triphosphates (column 13, line 32).

With regard to claim 19, Asada teaches primers (column 2, lines 48-54 and column 13, lines 50-53, for example).

With regard to claim 15, the recited instructions to not patentably distinguish over the kit taught by Asada. In *In re Ngai*, 70 USPQ2d 1862 (CAFC 2004), the court found that a claim directed to a kit for performing a method of normalizing and amplifying ribonucleic acids was properly rejected as anticipated by prior art, even though the content of the instructions in the claimed kit differed from the instructions in the prior art, since addition of a new set of instructions into the known kit merely teaches a new use for an existing product, in that the instructions do not interrelate with the kit so as to produce new product. Therefore, the addition of printed matter to an existing product will not distinguish an invention from the prior art in terms of patentability if the printed matter is not functionally related to product. See MPEP 2112.01(III).

Response to arguments

Applicant's arguments filed 11/10/2008 have been fully considered, but they are not persuasive. Although claim 15 has been amended to recite "*wherein said non-nucleic acid polyanion is provided at a molar concentration relative to said thermostable polymerase that reversibly inhibits said thermostable polymerase*", there is no requirement that the polymerase and the non-nucleic polyanion are provided together in a solution (unlike the case for claim 22). Hence, the limitation quoted above is construed as a recitation of intended use, which does not distinguish over the kit taught by Asada. That is, claim 15 is met merely by teaching a kit comprising the components listed. With such a kit, one would be able to mix the polymerase and the polyanion in any ratio desired.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asada et al (WO 00/14218, the March 16, 2000 publication of international application PCT/JP99/04815) as evidenced by Uemori et al (USPN 6,673,578). As the Asada reference was published in Japanese, USPN 6,673,578, which resulted from the national phase entry of PCT/JP99/04815 under 35 U.S.C. 371, will be used as an English translation, and all teachings will be pointed out with reference to the '578 patent.

The teachings of Asada have been discussed. Asada does not teach the particular molecular weights for the non-nucleic acid polyanion (i.e. "acidic substance") recited in claims 20 and 21.

It would have been *prima facie* obvious to arrive at the optimal molecular weights for the various types of "acidic substances" (dextran sulfate and the like), because Asada expressly suggests doing so (column 10, lines 10-24). Asada did in fact teach that the enhancement provided by the "acidic substance" (dextran sulfate and the like) was due to "holding the DNA polymerase on its molecule, thereby suppressing the non-specific interaction of the DNA polymerase to a template DNA, and of providing an

optimal amount of the DNA polymerase for the template. In other words, the DNA synthesis reaction efficiently progresses by optimizing the interaction between the template DNA and the DNA polymerase, the interaction increasing with the progress of the DNA synthesis reaction" (column 10, lines 32-38). Furthermore, Asada states (column 13, lines 14-18): "The acidic substance or the salt thereof as mentioned above efficiently allows to exhibit the DNA polymerase activity or to hold the enzyme, whereby the interaction between the DNA and the enzyme can be properly regulated." That is, Asada's purpose *was* to inhibit (reversibly) the DNA polymerase. Applicant's disclosure reads (paragraphs [0014] and [0017] of the published application):

"Surprisingly, conditions and parameters were found under with [*sic*] the strong inhibition of polynucleotide synthesis by sulfates polysaccharides is getting reversible with increasing temperatures."

"The present invention uses for the first time strong polyanionic polymerase inhibitors to control the activity of thermostable DNA polymerases dependent on the applied incubation temperature."

Hence, the goal of Asada, like that of Applicant, was to add these polyanionic compounds to polymerase in such a way as to regulate polymerase activity, allowing the polymerase to work at elevated temperature (i.e. PCR). Therefore, Asada's suggestion to optimize molecular weight of the polyanionic ("acidic") compounds is compatible with the claimed molecular weights (which presumably allow the polymerase to function at the elevated temperatures of PCR).

As set forth in MPEP 2144.05(II)(A):

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)"

Claims 22-34 and 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asada et al (WO 00/14218, the March 16, 2000 publication of international application PCT/JP99/04815) as evidenced by Uemori et al (USPN 6,673,578) and in view of Qiagen News (Issue No. 1, 1999, cover and pages 13-14). As the Asada reference was published in Japanese, USPN 6,673,578, which resulted from the national phase entry of PCT/JP99/04815 under 35 U.S.C. 371, will be used as an English translation, and all teachings will be pointed out with reference to the ‘578 patent.

With regard to claim 22, Asada teaches a kit (column 12, line 33) comprising a thermostable polymerase (column 12, lines 40-45 and line 58; “Taq” is Thermus aquaticus DNA polymerase, which is thermostable), a non-nucleic acid polyanion (“acidic substance”: column 13, lines 10-19 and column 9, lines 34-63; for example polyvinyl sulfates, polystyrene sulfates (column 9, line 38), sulfated-fucose-containing polysaccharides, dextran sulfate (column 9, lines 46-47)), and an appropriate polymerase reaction buffer (column 13, lines 31-34).

With regard to claims 23-25, Asada teaches optimization of the molecular weight of the polyanionic substances ("acidic substances") as discussed for claims 20 and 21 (column 10, lines 32-38).

With regard to claim 26, Asada teaches polyvinyl sulfate and polystyrene sulfate (column 9, lines 35-40).

With regard to claims 27-29, Asada teaches dextran sulfate, heparin, heparan sulfate, chondroitin sulfate (column 9, lines 45-50).

With regard to claims 30 and 31, Asada teaches optimizing the amount of the polyanionic (acidic) substance added (column 10, lines 29-33). Again, the goal of Asada, like that of Applicant, was to add these polyanionic compounds to polymerase reactions, yet allow the polymerase to work at elevated temperature (i.e. PCR). Therefore, Asada's suggestion to optimize amounts of the polyanionic ("acidic") compounds is compatible with the claimed amounts (which presumably allow the polymerase to function at the elevated temperatures of PCR). As set forth in MPEP 2144.05(II)(A):

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)"

With regard to claim 32, Asada teaches DNA polymerase ("Polymerase A", column 20, line 62; polymerase A is TaKaRa EX Taq DNA polymerase, see column 15, lines 41-49). Asada also teaches several other thermostable DNA polymerases (paragraph bridging columns 7-8).

With regard to claims 33, 34 and 44, Taq is derived from Thermus aquaticus, which is a thermophilic Eubacteria. Asada also teaches several other thermostable DNA polymerases (paragraph bridging columns 7-8).

With regard to claim 43, "optional" limitations (in this case, a separate container comprising a reaction buffer comprising monovalent cations between about 35-100 mM) are given no patentable weight. Nevertheless, Asada teaches exemplary conditions suitable for Taq polymerase comprising 50mM potassium chloride (potassium is a monovalent cation; see column 4, lines 30-35).

With regard to claim 45, Asada teaches dextran sulfate (column 9, lines 43-47).

With regard to claim 46, Asada teaches nucleotide 5'-triphosphates (column 13, line 32).

With regard to claim 47, Asada teaches primers (column 2, lines 48-54 and column 13, lines 50-53, for example).

Asada does not teach a "pre-inhibited thermostable polymerase", wherein the thermostable polymerase is reversibly bound to the non-nucleic acid polyanion in a storage buffer, as recited in claim 22. Nor does he expressly teach storing primers in a separate container. However, the only difference between what Asada teaches and the claimed invention is the storage of the polymerase and the polyanionic substance (i.e.

one of the "acidic substances" of Asada's disclosure) in one container. However, this cannot be considered a non-obvious difference because Asada explicitly teaches:

> "The above DNA polymerase, the acidic substance and other reagents may be contained in the kit in a state where each is present as an independent component, or a state in which some of the components are combined, including, for instance, a state in which the components are added to the reaction buffer and the like." (column 13, lines 34-39)

Furthermore, motivation to combine all components except primer and template into one reagent can be found in Qiagen News (Issue No. 1, 1999, cover and pages 13-14). This bulletin describes a product called HotStarTaq™ Master Mix Kit, which combines all of the components required for PCR amplification into one reagent:

> "HotStarTaq Master Mix is a ready-to-use mixture of HotStarTaq DNA Polymerase, QIAGEN PCR Buffer, and nucleotides. Setting up amplification reactions is fast and easy—simply pipet 25 µl of HotStarTaq Master Mix into each PCR tube and add 25 µl of your primers and template DNA in the PCR-quality water provided with the kit (Figure 2). The HotStarTaq Master Mix Kit provides easy handling with less pipetting, reducing the possibility of errors and contamination."

Note the mix also contains the magnesium required for the PCR reaction (see footnote to "Product" table, page 14).

It would have been *prima facie* obvious to one of ordinary skill in the art to combine the polymerase and polyanionic substance (acidic substance) taught by Asada into one container (producing a "storage buffer"), since Asada already suggested combining "some of the components" and since the Qiagen News article teaches the advantages of easy handling, less pipetting, and reduced possibility of errors and contamination. It would have been obvious to "pre-inhibit" the polymerase with the acidic substance, since Asada teaches that the addition of the acidic substance enhances the DNA synthesis reaction by "holding the DNA polymerase on its molecule, thereby suppressing the non-specific interaction of the DNA polymerase to a template

DNA, and of providing an optimal amount of the DNA polymerase for the template. In other words, the DNA synthesis reaction efficiently progresses by optimizing the interaction between the template DNA and the DNA polymerase, the interaction increasing with the progress of the DNA synthesis reaction" (column 10, lines 32-38, emphasis provided). This language implies that acidic substance was initially supposed to be inhibit (hold, suppress) the polymerase.

Furthermore, in the context of a kit, one would have been motivated *not* to put the primers into the same container as the polymerase and polyanionic substance. Keeping the polymerase reagent free of any primers would allow the use of the polymerase reagent to be used in reactions for different nucleic acids targets. On the contrary, if one made the kit with the primers already added to the polymerase reagent, then one would have been limited to reactions with only those primers.

Response to arguments

Applicant's arguments filed 11/10/2008 have been fully considered but are not persuasive. Applicant argues that Asada is teaching something directly opposite to Applicant's disclosure. However, after a careful review of both documents, it appears that Applicant's disclosure and Asada's disclosure are both relying on the ability of the acidic substance (polyanionic substance) to sequester the polymerase and thereby inhibit or suppress its activity:

Applicant's specification paragraph [0017]: "The present invention uses for the first time strong polyanionic polymerase inhibitors to control the activity of thermostable DNA polymerases dependent on the applied incubation temperature."

Asada's disclosure column 13, lines 14-18: "The acidic substance or the salt thereof as mentioned above efficiently allows to exhibit the DNA polymerase activity or to hold the enzyme, whereby the interaction between the DNA and the enzyme can be properly regulated."

Asada's disclosure column 10, lines 32-38: "The action of the acidic substance is not particularly limited, and it is considered to be on the bases of holding the DNA polymerase on its molecule, thereby suppressing the non-specific interaction of the DNA polymerase to a template DNA…"

Asada's disclosure, column 9, lines 7-13: "…excess DNA polymerase is trapped with the acidic substance during the DNA synthesis reaction…".

The only apparent difference in this aspect of the disclosures is that Asada does not expressly implicate increased temperature as the reason why inhibition is reversed. However, this difference is irrelevant because the instant claims are drawn to products, not methods. Both Applicant's and Asada's disclosures were concerned with successfully conducting PCR in the presence of these acidic/polyanionic compounds. Both disclosures made use of the inhibitory properties of such compounds on polymerases. Therefore, there was a reason based on Asada's disclosure to make the claimed products.

Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Asada et al (WO 00/14218, the March 16, 2000 publication of international application PCT/JP99/04815) as evidenced by Uemori et al (USPN 6,673,578) and in view of

Qiagen News (Issue No. 1, 1999, cover and pages 13-14) as applied to claims 22-34 and 43-47 above, and further in view of Tonoike et al (US 6,472,187). As the Asada reference was published in Japanese, USPN 6,673,578, which resulted from the national phase entry of PCT/JP99/04815 under 35 U.S.C. 371, will be used as an English translation, and all teachings will be pointed out with reference to the '578 patent.

The teachings of Asada and Qiagen News have been discussed. These references do not teach the reverse transcriptases recited in claim 35.

Tonoike teaches amplification of RNA using AMV reverse transcriptase (column 5, line 45). The reverse transcriptase reaction was performed at 55°C (column 6, lines 50-55). This, together with the fact that AMV is specifically recited in claim 35, evidences that AMV RT is "thermostable". The reaction was conducted in the presence of heparin (column 6, line 45). In fact, Tonoike expressly teaches to use sulfated polysaccharides such as heparin, heparan sulfate, chondroitin sulfate, fucoidan and dextran sulfate (column 4, lines 45-50).

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the solution suggested by the combined teachings of Asada and Qiagen News to include AMV reverse transcriptase in order to allow for RNA amplification as disclosed by Tonoike, since both the PCR taught by Asada, and the reverse transcription and PCR taught by Tonoike, were expressly recommended to be carried out in the presence of the specific polyanionic substances recited in Applicant's claims. One would have been motivated to arrive at such a "stock solution", since Asada already suggested

combining "some of the components" and since the Qiagen News article teaches the advantages of easy handling, less pipetting, and reduced possibility of errors and contamination.

Conclusion

No claims are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637